

PATENT ABSTRACTS OF JAPAN

[Date of requesting appeal against examiner's decision of rejection]
[Date of extinction of right]

18.03.2003

(11)Publication number : 2001-296288
(43)Date of publication of application : 26.10.2001

(51)Int.Cl.

G01N 30/48
G07B 57/00
G07C 29/76
G07C 33/40
G07C 45/79
G07C 49/83

(21)Application number : 2000-116437 (71)Applicant : DAICEL CHEM IND LTD
(22)Date of filing : 18.04.2000 (72)Inventor : ONISHI ATSUSHI
FUTAGAWA TORU

(54) FILLER FOR OPTICAL ISOMER SEPARATION FOR LIQUID CHROMATOGRAPHY

(57)Abstract:

PROBLEM TO BE SOLVED: To provide a filler and a column for liquid chromatography, giving superior optical isomer separation relative to an object compound.
SOLUTION: In this filler for optical isomer separation for liquid chromatography, made of a polysaccharide derivative carrying filler as a main component and a column in which the filler is filled, a TS coefficient defined by the following formula (I) is in the range of 0.25 to 1.0. TS coefficient=[Vc-[(TS)-(blank)] x FR]/[(t(TS)-t(blank))] x ER (I) [In the formula, abbreviations mean Vc (cm³): a column volume, FR (ml/min.): a flow velocity, t (TS) (min.): an elution time of Tetrakis(trimethylsilyl)silane(=TS), and t(blank)Xmin.): elution time for TS in the state with the column not connected].

LEGAL STATUS

[Date of request for examination] 18.04.2000
[Date of sending the examiner's decision of rejection] 18.02.2003

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number] 3635002

[Date of registration] 07.01.2005

[Number of appeal against examiner's decision of rejection] 2003-04420

Copyright (C): 1998,2003 Japan Patent Office

* NOTICES *

JPO and NCIPJ are not responsible for any damages caused by the use of this translation.

- 1.This document has been translated by computer. So the translation may not reflect the original precisely.
- 2.*** shows the word which can not be translated.
- 3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]

[Claim 1] The bulking agent for optical-isomer separation for liquid chromatography characterized by the range of TS multiplier defined by the bottom type (I) obtained using the column for optical-isomer separation for liquid chromatography which filled up column tubing with the bulking agent concerned by the slurry filling-up method in the bulking agent for optical-isomer separation for liquid chromatography which uses a polysaccharide derivative support bulking agent as a main component being 0.25 to 1.0.

$$TS \text{ multiplier} = [V_c - (t(TS) - t(\text{blank})) \times FR] / [(t(TS) - t(\text{blank})) \times FR (I)]$$

[— the elution time amount of TS in the condition of not connecting the elution time amount t (blank) (min.); column of V_c (cm³); column volume FR (ml/min.); rate-of-flow t(TS) (min.); Tetrakis (trimethylsilyl) silane (= TS) is shown among a formula.]

[Claim 2] The bulking agent for optical-isomer separation according to claim 1 for liquid chromatography whose polysaccharide derivative is the ester derivative or carbamate derivative of a cellulose or an amylose.

[Claim 3] The bulking agent for optical-isomer separation according to claim 1 for liquid chromatography which is a bulking agent with which the column for analysis used for the purpose of optical-purity measurement is presented.

[Claim 4] The bulking agent for optical-isomer separation according to claim 1 for liquid chromatography which is a bulking agent with which the column for preparative isolation used for the aliquot of the single column method aiming at optically-active-substance acquisition is presented.

[Claim 5] The bulking agent for optical-isomer separation according to claim 1 for liquid chromatography which is a bulking agent with which the column for preparative isolation of continuous system liquid chromatography is presented.

[Claim 6] The column for optical-isomer separation for liquid chromatography characterized by the range of TS multiplier defined by the formula (I) according to claim 1 being 0.25 to 1.0 in the column for optical-isomer separation for liquid chromatography which uses a polysaccharide derivative support bulking agent as a main component.

[Claim 7] The column for optical-isomer separation according to claim 6 for liquid chromatography whose polysaccharide derivative is the ester derivative or carbamate derivative of a cellulose or an amylose.

[Claim 8] The column for optical-isomer separation according to claim 6 for liquid chromatography which is a column for analysis used for the purpose of optical-purity measurement.

[Claim 9] The column for optical-isomer separation according to claim 6 for liquid

chromatography which is a column for preparative isolation used for the aliquot of the single column method aiming at optically-active-substance acquisition.

[Claim 10] The column for optical-isomer separation according to claim 6 for liquid chromatography which is a column for preparative isolation of continuous system liquid chromatography.

[Translation done.]

★ NOTICES ★

JP0 and NCIP1 are not responsible for any damages caused by the use of this translation.

1. This document has been translated by computer. So the translation may not reflect the original precisely.
2. *** shows the word which can not be translated.
3. In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention] This invention relates to the optical-isomer analytical skill which has a high separation factor and carries out optical resolution of the broad chiral compound in analysis of drugs, food, agricultural chemicals, perfume, etc. especially about the bulking agent and column which are used for separation of an optical isomer, especially separation of the optical isomer by the liquid chromatography method.

[0002]

[Description of the Prior Art] Although physical properties, such as chemical property, for example, the boiling point, the melting point, and solubility, are completely the same, many physical and optical isomers with which a difference is seen by bioactive exist in an organic compound. The living body consists of protein which consists of L-amino acid, and the difference of recognition of the organic compound by the high order dissymmetry space which these protein builds discovers him as a bioactive difference. The difference in the pharmacological activity by the ease of carrying out of association with a specific acceptor in the living body is often studied, and drug effect and the case where a remarkable difference is seen in respect of toxicity are well known for the case of drugs between optical isomers. For this reason, the Ministry of Health and Welfare has indicated Drug Approval and Licensing Procedures when the drug concerned is racemic modification, it is "desirable" to examine absorption, distribution, a metabolic turnover, and an elimination moving state about each isomer.

[0003] As stated previously, research of the physical and the technique of analyzing the optical isomer of a broad class with a simple and sufficient precision since physical properties, such as chemical property, for example, the boiling point, the melting point, and solubility, are completely the same, and it cannot analyze with the usual separation means of an optical isomer was done energetically. And the optical-resolution method by high performance liquid chromatography (HPLC), especially the optical-resolution approach by the chiral column for HPLC progressed as tools of analysis which meet these demands. With the chiral column said here, the chiral stationary phase which made the dissymmetry discernment agent itself or the dissymmetry discernment agent support on suitable support is used. For example, the ovomucoid (JP.63-307829 A) which are optical-activity polymethacrylic acid triphenylmethyl (refer to JP.57-150432 A), a cellulose or an amylose derivative (Y. Okamoto, M.Kawashima and K.Hatada, J.Am.Chem.Soc., 106, 5337, 1984), and protein is developed.

[0004] It is known that the column for optical resolution which made the cellulose or the amylose derivative support on silica gel also in the chiral stationary phase for HPLC of these many has high dissymmetry discernment ability to a very broad compound, and examination of the optically-active-substance liquid chromatography method aliquot in the industrial scale which combined such chiral stationary phases for HPLC and a false moving-bed method is further advanced in recent years (12 Phram Tech Japan, vol. 43 (1996)).

[0005] In order to raise the basis of such backgrounds, and chromatography preparative isolation productivity, the chiral stationary phase which gives good separation of a piece is increasingly called for from the purpose compound, and the device which acquires high chromatography

effectiveness boils many things, and it is put.

[0006]

[Means for Solving the Problem] this invention persons reached this invention, as a result of inquiring wholeheartedly about the bulking agent for optical-isomer separation which made the polysaccharide derivative the dissymmetry discernment agent.

[0007] That is, this invention offers the bulking agent for optical-isomer separation for liquid chromatography characterized by for the range of TS multiplier defined by the bottom type (I) obtained using the column for optical-isomer separation for liquid chromatography which filled up column tubing with the bulking agent concerned by the slurry filling-up method to be 0.25 to 1.0, and the column which filled up the list with this in the bulking agent for optical-isomer separation for liquid chromatography which uses a polysaccharide derivative support bulking agent as a main component.

[0008]

TS multiplier = $[V_c - \{t(TS) - t(\text{blank})\}] \times FR / [t(TS) - t(\text{blank})] \times FR (I)$

[— the elution time amount of TS in the condition of not connecting the elution time amount t (blank) (min.); column of Vc (cm³); column volume FR (ml/min.); rate-of-flow t(TS) (min.); Tetrakis (trimethylsilyl) silane (= TS) is shown among a formula.]

[0009]

[Embodiment of the Invention] Hereafter, the gestalt of operation of this invention is explained to a detail.

[0010] The polysaccharide derivative used for this invention is obtained by making a polysaccharide and the compound which has the hydroxyl group and the functional group which can react react.

[0011] Although either a synthetic polysaccharide, a natural polysaccharide and a natural product conversion polysaccharide may not be asked as a polysaccharide used for this invention, but what kind of thing may be used as long as it is optical activity, the high thing of the desirable regularity of a joint format is desirable, if it illustrates — beta-1, 4-glucan (cellulose), and alpha-1, 4-glucan (an amylose —) An amylopectin, alpha-1, 6-glucan (dextran), beta-1, 6-glucan (BUSUTSURAN), Beta-1, 3-glucan (for example, curdlan, sizofiran, etc.), alpha-1, 3-glucan, beta-1, 2-glucan (Crown Gall polysaccharide) beta-1, 4-galactan, beta-1, 4-mannan, alpha-1, 6-mannan, beta-1, 2-cell tongue (inulin). It is beta-2, 6-cell tongue (levan) beta-1, 4-xylan, beta-1, 3-xylan, beta-1, 4-chitosan, alpha-1, 4-N-acetyl chitosan (chitin), a pullulan, agarose, an alginate acid, etc., and the starch containing an amylose is also contained. In these, the cellulose which can obtain the polysaccharide of a high grade easily, an amylose, beta-1, 4-xylan, beta-1, 4-chitosan, a chitin, beta-1, 4-mannan, an inulin, curdlan, etc. are desirable, and especially a cellulose and an amylose are desirable.

[0012] Although the number average degree of polymerization (the pyranose contained in 1 molecule or the number of averages of a furanose ring) of these polysaccharides is ten or more preferably five or more and especially an upper limit does not have it, it is desirable that it is 1000 or less in respect of the ease of handling.

[0013] Moreover, if it is an isocyanic acid derivative, a carboxylic acid, ester, acid halide, an acid-amide compound, a halogenated compound, an aldehyde, alcohol, or the compound that has a leaving group in addition to this as a compound which has a hydroxyl group and the functional group which can react, what kind of thing may be used and has an aliphatic series, an alicyclic group, aromatic series, and a hetero aromatic compound can be used. Especially a desirable thing is the carbamate derivative or ester derivative of a polysaccharide which has 0.1 or more the urethane bonds or ester bonds per 1 glucose unit as a polysaccharide derivative used for this invention.

[0014] With the polysaccharide derivative support bulking agent of this invention, the polysaccharide derivative made to apply on support is used for a raw material. The chemical bond between support and the applied polysaccharide derivative, the chemical bond of the polysaccharide derivatives on support. By the radical reaction using a reaction, a radical initiator, etc. which are caused by the electromagnetic wave exposure of radiation irradiation, such as a chemical bond which used the third component, an optical exposure to the polysaccharide

derivative on support, and a gamma ray, microwave, etc. etc. The bulking agent to which firmer immobilization was given by making the further chemical bond form is also contained. Not using the polysaccharide derivative made to apply on support furthermore, the polysaccharide derivative support bulking agent produced by the approach of carrying out the chemical bond of a polysaccharide or a polysaccharide derivative, and the support, such as silica gel, directly is also contained. Moreover, the bulking agent for optical-isomer separation which uses a polysaccharide derivative support bulking agent as a main component means mixture with the bulking agent which are not objects for optical-isomer separation, such as an above-mentioned polysaccharide derivative support bulking agent, a bulking agent for optical-isomer separation of other type, or silica gel by which octadecyl surface treatment was carried out, for example.

[0015] As support used for this invention, porosity organic support or porosity inorganic support is mentioned, and it is porosity inorganic support preferably. A thing suitable as porosity organic support is a high polymer which consists of polystyrene, polyacrylamide, polyacrylate, etc., and things suitable as porosity inorganic support are a silica, an alumina, a magnesia, glass, a kaolin, titanium oxide, a silicate, hydroxyapatite, etc. Especially desirable support is silica gel, 0.1 micrometers - 10nm of particle size of silica gel is 1 micrometer - 300 micrometers preferably, and 10A - 100 micrometers of average apertures are 50A - 50000A preferably. In order to eliminate the effect of a residual silanol, as for a front face, it is desirable to perform surface treatment, but it is satisfactory even if surface treatment is not performed at all.

[0016] The elution time amount of the tetrakis (trimethylsilyl) silane (it is called Following TS) in the condition of not connecting with the condition of having connected the column to liquid chromatograph equipment in TS multiplier calculation in this invention is measured, and TS multiplier defined by the above-mentioned formula (I) is computed using the acquired elution time amount. Although the analysis apparatus used in the case of this measurement has RI detector, a UV detector, etc. which can check the elution of TS as a detector which is HPLC equipment and is used, it is desirable to detect on the wavelength of 210nm using a UV detector especially.

[0017] As analysis conditions, it carries out on normal phase conditions, i.e., the mobile phase conditions which use a hydrophobic solvent as a main component. Specifically, it is the mobile phase of the presentation ratio of n-hexane / 2-propanol $\approx 9 / 1$ (v/v). Moreover, analysis temperature is a room temperature (25 degrees C), and, as for the rate of flow, 1/1, especially 4.15 of the quadrant of column volume Vc (cm³) - 9 minutes, i.e., [Vcx(1/4 15)] ml/min., are desirable. It is still more desirable the amount of volume of 1/300 - 1/600 of column volume and for the amount of placing of TS to drive in especially TS solution made to dissolve TS in a mobile phase by 5.0mg [ml] concentration the amount of volume of 1/415, i.e., [Vcx(1/415)] ml.

[0018] In this invention, if it is required for the range of TS multiplier computed as mentioned above to be 0.25 to 1.0 and it separates from this range, good separability ability cannot be obtained.

[0019] Although it is common to use for the optical-isomer separation by a chromatography method and membrane separation, such as a gas chromatography, liquid chromatography, supercritical chromatography, thin-layer chromatography, and capillary electrophoresis, as for the bulking agent of this invention, applying to especially a liquid chromatography method is desirable.

[0020] Furthermore, the bulking agent of this invention is preferably used for the column for analysis of the liquid chromatography used mainly for the purpose of optical-purity measurement. the column for preparative isolation of the liquid chromatography of the single column method aiming at several mg - several kg optically-active-substance acquisition, the column for preparative isolation of the continuous system liquid chromatography represented by the simulated moving bed method, etc.

[0021]

[Example] Hereafter, although an example explains this invention to a detail, this invention is not limited to these examples.

[0022] Example 1TS multiplier = amylose of 0.527 Aminopropyl silanizing (APS processing) was performed by making the production approach ** silica gel surface treatment porosity silica gel

(particle size of 20 micrometers, 1300A of average pore size) of the bulking agent for tris (3, 5-dimethylphenyl carbamate) support optical-isomer separation react with 3-aminopropyl triethoxysilane by the well-known approach. The silica gel with which carbamoyl surface treatment was performed was obtained at reacting the obtained APS processing silica gel with 3 and 5-dimethylphenyl isocyanate.

[0023] ** amylose bottom of synthetic nitrogen-gas-atmosphere mind of tris (3, 5-dimethylphenyl carbamate), and amylose 10.0g --- desiccation pyridine 360ml --- inside and under 3 and 5-dimethylphenyl isocyanate 82.2g (3Eq) and pyridine reflux temperature, it poured into methanol 6.0L, after performing heating stirring for 60 hours. The depositing solid-state was separated with the glass filter, and performed the vacuum drying (80 degrees C, 5 hours) after several washing with the methanol. Consequently, 35.3g (95%) of white solid-states which were yellowish a little was obtained.

[0024] ** Amylose obtained by the support above-mentioned ** to the silica gel of tris (3, 5-dimethylphenyl carbamate) Tris (3, 5-dimethylphenyl carbamate) 10g was dissolved in 100ml of ethyl acetate, and the moiety of this polymer dope was applied to homogeneity at silica gel 40g of **. It is the target amylose by performing reduced pressure drying for 20 minutes on condition that 50 degrees C and 120Torr, remaining ethyl acetate further, and performing reduced pressure drying for 20 minutes for a moiety on the same conditions (50 degrees C, 120Torr) as the point after homogeneity spreading similarly after spreading. The tris (3, 5-dimethylphenyl carbamate) support mold bulking agent was obtained.

[0025] ** Amylose produced by packed column production ** for HPLC from a production bulking agent Using the separating medium which supported tris (3, 5-dimethylphenyl carbamate) on silica gel as a bulking agent, the column made from stainless steel with a die length [of 25cm] and a bore of 0.46cm was filled up with the slurry filling-up method, and the separation column for optical isomers was produced.

[0026] Example 2TS multiplier = amylose of 0.926 Carbamoyl surface treatment was performed to porosity silica gel (particle size of 20 micrometers, 1300A of average pore size) as well as ** of the production approach ** silica gel surface treatment example 1 of the bulking agent for tris (3, 5-dimethylphenyl carbamate) support optical-isomer separation.

[0027] ** Amylose By the same technique as ** of the synthetic example 1 of tris (3, 5-dimethylphenyl carbamate), it is an amylose. Tris (3, 5-dimethylphenyl carbamate) was produced. [0028] ** Amylose Amylose obtained by the support above-mentioned ** to the silica gel of tris (3, 5-dimethylphenyl carbamate) Tris (3, 5-dimethylphenyl carbamate) 52.5g was dissolved in 489ml of ethyl acetate, and 1/4 amount of this polymer dope was applied to homogeneity at silica gel 97.5g of **. Reduced pressure drying for 15 minutes was performed for ethyl acetate on condition that 50 degrees C and 120Torr after spreading, and reduced pressure drying for 15 minutes was similarly performed for 1/4 amount to the pan on the same conditions (50 degrees C, 120Torr) as the point after homogeneity spreading. It is the target amylose by carrying out reduced pressure drying of the 1/4 amount for 45 minutes on these conditions (50 degrees C, 120Torr) after homogeneity spreading succeeding, remaining at the end and carrying out reduced pressure drying of the 1/4 amount for 45 minutes on these conditions (50 degrees C, 120Torr) after homogeneity spreading. The tris (3, 5-dimethylphenyl carbamate) support mold bulking agent was obtained.

[0029] ** Amylose produced by packed column production ** for HPLC from a production bulking agent Using the separating medium which supported tris (3, 5-dimethylphenyl carbamate) on silica gel as a bulking agent, the column made from stainless steel with a die length [of 25cm] and a bore of 0.46cm was filled up with the slurry filling-up method, and the separation column for optical isomers was produced.

[0030] Example 3TS multiplier = amylose of 0.286 Carbamoyl surface treatment was performed to porosity silica gel (particle size of 20 micrometers, 1300A of average pore size) as well as ** of the production approach ** silica gel surface treatment example 1 of the bulking agent for tris (3, 5-dimethylphenyl carbamate) support optical-isomer separation.

[0031] ** Amylose By the same technique as ** of the synthetic example 1 of tris (3, 5-dimethylphenyl carbamate), it is an amylose. Tris (3, 5-dimethylphenyl carbamate) was produced.

[0032] ** Amylose Amylose obtained by the support above-mentioned ** to the silica gel of tris (3, 5-dimethylphenyl carbamate) Tris (3, 5-dimethylphenyl carbamate) 1.25g was dissolved in 12.5ml of ethyl acetate, and the whole quantity of this polymer dope was applied to homogeneity at silica gel 11.25g of **. It is the target amylose by performing reduced pressure drying for 15 minutes for ethyl acetate on condition that 50 degrees C and 120Torr after spreading. The tris (3, 5-dimethylphenyl carbamate) support mold bulking agent was obtained.

[0033] ** Amylose produced by packed column production ** for HPLC from a production bulking agent Using the separating medium which supported tris (3, 5-dimethylphenyl carbamate) on silica gel as a bulking agent, the column made from stainless steel with a die length [of 25cm] and a bore of 0.46cm was filled up with the slurry filling-up method, and the separation column for optical isomers was produced.

[0034] Example 4TS multiplier = amylose of 0.698 Carbamoyl surface treatment was performed to porosity silica gel (particle size of 20 micrometers, 1300A of average pore size) as well as ** of the production approach ** silica gel surface treatment example 1 of the bulking agent for tris (3, 5-dimethylphenyl carbamate) support optical-isomer separation.

[0035] ** Amylose By the same technique as ** of the synthetic example 1 of tris (3, 5-dimethylphenyl carbamate), it is an amylose. Tris (3, 5-dimethylphenyl carbamate) was produced.

[0036] ** Amylose Amylose obtained by the support above-mentioned ** to the silica gel of tris (3, 5-dimethylphenyl carbamate) Tris (3, 5-dimethylphenyl carbamate) 50.25g was dissolved in 437.2ml of ethyl acetate, and 1/3 amount of this polymer dope was applied to homogeneity at silica gel 117.25g of **. Reduced pressure drying for 15 minutes was performed for ethyl acetate on condition that 50 degrees C and 120Torr after spreading. It is the target amylose by carrying out 1/3 amount of a polymer dope after spreading, carrying out reduced pressure drying of the ethyl acetate for 15 minutes on these conditions similarly succeeding, remaining, performing the homogeneity spreading back for 1/3 amount, and performing reduced pressure distilling off for ethyl acetate by the reduced pressure drying for 25 minutes. The tris (3, 5-dimethylphenyl carbamate) support mold bulking agent was obtained.

[0037] ** Amylose produced by packed column production ** for HPLC from a production bulking agent Using the separating medium which supported tris (3, 5-dimethylphenyl carbamate) on silica gel as a bulking agent, the column made from stainless steel with a die length [of 25cm] and a bore of 0.46cm was filled up with the slurry filling-up method, and the separation column for optical isomers was produced.

[0038] Example 5TS multiplier = amylose of 0.379 Carbamoyl surface treatment was performed to porosity silica gel (particle size of 20 micrometers, 1300A of average pore size) as well as ** of the production approach ** silica gel surface treatment example 1 of the bulking agent for tris (3, 5-dimethylphenyl carbamate) support optical-isomer separation.

[0039] ** Amylose By the same technique as ** of the synthetic example 1 of tris (3, 5-dimethylphenyl carbamate), it is an amylose. Tris (3, 5-dimethylphenyl carbamate) was produced.

[0040] ** Amylose Amylose obtained by the support above-mentioned ** to the silica gel of tris (3, 5-dimethylphenyl carbamate) Tris (3, 5-dimethylphenyl carbamate) 27.0g was dissolved in 270ml of ethyl acetate, and 1/2 amount of this polymer dope was applied to homogeneity at silica gel 153.0g of **. Reduced pressure drying for 15 minutes was performed for ethyl acetate on condition that 50 degrees C and 120Torr after spreading. They are the reduced pressure drying for 15 minutes, and the target amylose at these conditions after spreading and about ethyl acetate similarly in 1/2 amount of a polymer dope succeeding, the tris (3, 5-dimethylphenyl carbamate) support mold bulking agent was obtained.

[0041] ** Amylose produced by packed column production ** for HPLC from a production bulking agent Using the separating medium which supported tris (3, 5-dimethylphenyl carbamate) on silica gel as a bulking agent, the column made from stainless steel with a die length [of 25cm] and a bore of 0.46cm was filled up with the slurry filling-up method, and the separation column for optical isomers was produced.

[0042] Example of comparison 1TS multiplier = 1.050 amyloses Carbamoyl surface treatment was performed to porosity silica gel (particle size of 20 micrometers, 1300A of average pore size) as well as ** of the production approach ** silica gel surface treatment example 1 of the bulking

agent for tris (3, 5-dimethylphenyl carbamate) support optical-isomer separation.

[0043] ** Amylose By the same technique as ** of the synthetic example 1 of tris (3, 5-dimethylphenyl carbamate), it is an amylose. Tris (3, 5-dimethylphenyl carbamate) was produced.

[0044] ** Amylose Amylose obtained by the support above-mentioned ** to the silica gel of tris (3, 5-dimethylphenyl carbamate) Tris (3, 5-dimethylphenyl carbamate) 2.5g was dissolved in 18.75ml of ethyl acetate, and 1/4 amount of this polymer dope was applied to homogeneity at silica gel 3.75g of **. Reduced pressure drying for 15 minutes was performed for ethyl acetate on condition that 50 degrees C and 120Torr after spreading. Succeedingly, the spreading back was performed for 1/4 amount of a polymer dope, and reduced pressure drying for 30 minutes was similarly performed for ethyl acetate on these conditions. Furthermore, it is the target amylose by performing the spreading back for 1/4 amount of a polymer dope, performing reduced pressure drying for 30 minutes for ethyl acetate on these conditions similarly, remaining, performing the spreading back for the polymer dope of 1/4 amount, and performing reduced pressure drying for 60 minutes for ethyl acetate on these conditions similarly. The tris (3, 5-dimethylphenyl carbamate) support mold bulking agent was obtained.

[0045] ** Amylose produced by packed column production ** for HPLC from a production bulking agent Using the separating medium which supported tris (3, 5-dimethylphenyl carbamate) on silica gel as a bulking agent, the column made from stainless steel with a die length [of 25cm] and a bore of 0.46cm was filled up with the slurry filling-up method, and the separation column for optical isomers was produced.

[0046] Example of comparison 2TS multiplier = amylose of 0.240 Carbamoyl surface treatment was performed to porosity silica gel (particle size of 20 micrometers, 1300A of average pore size) as well as ** of the production approach ** silica gel surface treatment example 1 of the bulking agent for tris (3, 5-dimethylphenyl carbamate) support optical-isomer separation.

[0047] ** Amylose By the same technique as ** of the synthetic example 1 of tris (3, 5-dimethylphenyl carbamate), it is an amylose. Tris (3, 5-dimethylphenyl carbamate) was produced.

[0048] ** Amylose Amylose obtained by the support above-mentioned ** to the silica gel of tris (3, 5-dimethylphenyl carbamate) Tris (3, 5-dimethylphenyl carbamate) 125.0g was dissolved in 1250ml of ethyl acetate, and the whole quantity of this polymer dope was applied to homogeneity at the 2375.0 g silica gel of **. The target amylose tris (3, 5-dimethylphenyl carbamate) support mold bulking agent was obtained after spreading by performing reduced pressure drying for 10.5 minutes for ethyl acetate on condition that 50 degrees C and 120Torr.

[0049] ** Amylose produced by packed column production ** for HPLC from a production bulking agent Using the separating medium which supported tris (3, 5-dimethylphenyl carbamate) on silica gel as a bulking agent, the column made from stainless steel with a die length [of 25cm] and a bore of 0.46cm was filled up with the slurry filling-up method, and the separation column for optical isomers was produced.

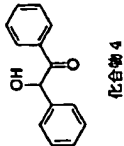
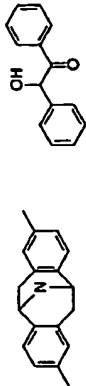
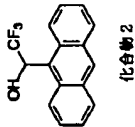
[0050] Amylose produced in the application examples 1-5 and the examples 1-2 of a comparison Using the column for optical-isomer separation for HPLC filled up with the bulking agent which supported tris (3, 5-dimethylphenyl carbamate) on silica gel, the elution time amount [t (TS) (min.)] of TS was measured by the liquid chromatography method of the following conditions, and TS multiplier was computed by the following formula. A result is shown in Table 1.

<Analysis condition of liquid chromatography> mobile phase: n-hexane / 2-propanol =9 / 1 (v/v) rate-of-flow: -- 1.0 ml/min. temperature: -- 25-degree-C detection: -- 210nm placing TS concentration: -- 5.0mg (mobile phase)/ml

The amount of TS placing : 10microlCTS multiplier formula >Vc:0.23x0.23x3.14x25=4.15cm3. HPLC produced in examples 1-5 and the examples 1-2 of a comparison to [4.15-{t(TS)-0.16} x1.0] / [t(TS)-0.16] x1.0 pan is used. Optical resolution of the compounds 1-4 expressed with the following formula which is racemic modification was performed, and the degree-of-separation Rs value which is the index which shows extent of separation of each optically active substance was computed by the following type. The result is also shown in Table 1.

[0051]

[Formula 1]



[0052] $R_s=2(t_1-t_2)/(W_1+W_2)$
(Here, t_1 and t_2 show W_1 and the elution time amount of each optical isomer and W_2 show the peak width of an optical-isomer peak.)

[0053]

[Table 1]

HPLC用 カラム	TS (min)	TS 値	分 離 度 (R_s)			
			化合物1	化合物2	化合物3	化合物4
1	2.87	0.927	4.81	1.66	1.88	1.77
2	2.16	0.926	3.40	1.06	1.44	1.12
3	3.14	0.288	3.65	1.03	1.21	1.50
4	2.42	0.696	3.95	1.21	1.63	1.34
5	2.84	0.379	5.49	1.38	1.90	1.91
比 例	1	2.03	1.050	2.17	0.63	1.01
	2	3.25	0.240	0.58	0.65	1.21

[0054] Moreover, the relation between TS multiplier of a bulking agent and R_s value of a compound 1 was shown in drawing 1, and the relation between TS multiplier of a bulking agent and R_s value of compounds 2-4 was shown in drawing 2.

[0055] From the above result, the bulking agent which has TS multiplier in the range of 0.25 to 1.0 is understood that the separability ability of an optical isomer is good.

[Translation done.]

* NOTICES *

JPO and NCIP1 are not responsible for any damages caused by the use of this translation.

1.This document has been translated by computer. So the translation may not reflect the original precisely.

2.*** shows the word which can not be translated.

3.In the drawings, any words are not translated.

DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]

[Drawing 1] It is drawing showing the relation between TS multiplier of a bulking agent, and Rs value of a compound 1.

[Drawing 2] It is drawing showing the relation between TS multiplier of a bulking agent, and Rs value of compounds 2-4.

[Translation done.]

(19)日本国特許庁 (J P) (12) 公開特許公報 (A)

(11)特許出願公開番号

特開2001-296288
(P2001-296288A)

(43)公開日 平成13年10月26日(2001.10.26)

(51)IntCl. ⁷	識別記号	P I	チヨウド(参考)
G 0 1 N 30/48		G 0 1 N 30/48	W 4 H 0 0 6
C 0 7 B 57/00	3 4 0	C 0 7 B 57/00	N
	3 4 3		3 4 3
	3 5 0		3 5 0

審査請求 有 請求項の数10 O L (全 8 頁) 最終頁に続く

(21)出願番号	特開2000-116437(P2000-116437)	(71)出願人	000002901
(22)公開日	平成12年4月18日(2000.4.18)	ダイセル化学工業株式会社 大阪府堺市東区東町1番地	
		(72)発明者	大西 敏
		(72)発明者	栗坂つとむ 佐千現 I 丁目14-14
		(72)発明者	三川 亨
		(72)発明者	兵庫県姫路市飾区今在家4丁目85-1-301
		(74)代理人	100063897
		弁理士	古谷 豊 (外 3 名)
		Fターム(参考)	41006 A02 ACB AD17 FCS4 FE11 FE71 FE74

(54)【発明の名称】 液体クロマトグラフィー用光学異性体分離用充填剤

(57)【要約】

【課題】 目的化合物に対して、良好な光学異性体分離を与える液体クロマトグラフィー用充填剤及びカララムの提供。

【解決手段】 多機能誘導体担持充填剤を主たる構成要素

とする液体クロマトグラフィー用光学異性体分離用充填剤並びにこれを充填したカララムにおいて、下式(1)で定義されるT S低数が0.25から1.0の範囲である。

$$\text{T S低数} = \frac{[\text{t}(\text{TS}) - \text{t}(\text{blank})]}{[\text{FR}]} \times \text{FR} \quad (1)$$

式中、Vc (cm³) : カラム体積、FR (ml/min.) : 流速、t (TS) (min.) : Tetrakis(trimethylsilyl)silane(逆、t (TS) (min.) : カラムを保持時間を示す。)

【特許請求の範囲】

【請求項1】 多機能誘導体担持充填剤を主たる構成要素とする液体クロマトグラフィー用光学異性体分離用充填剤において、当該充填剤をスラリー充填法によりカララムに充填する。

$$\text{T S低数} = \frac{[\text{t}(\text{TS}) - \text{t}(\text{blank})]}{[\text{FR}]} \times \text{FR} \quad (1)$$

式中、Vc (cm³) : カラム体積

FR (ml/min.) : 流速

t (TS) (min.) : Tetrakis(trimethylsilyl)silane(逆、t (TS) (min.) : カラムを保持時間を示す。)

【請求項2】 多機能誘導体担持充填剤を主たる構成要素とする液体クロマトグラフィー用光学異性体分離用充填剤において、当該充填剤をスラリー充填法によりカララムに充填する。

【請求項3】 光学異性体分離を目的とする分析用カララムに供される充填剤である請求項1記載の液体クロマトグラフィー用光学異性体分離用充填剤。

【請求項4】 光学異性体分離を目的とする分析用カララムに供される充填剤である請求項1記載の液体クロマトグラフィー用光学異性体分離用充填剤。

【請求項5】 逆相式液体クロマトグラフィーの分離用カララムに供される充填剤である請求項1記載の液体クロマトグラフィー用光学異性体分離用充填剤。

【請求項6】 多機能誘導体担持充填剤を主たる構成要素とする液体クロマトグラフィー用光学異性体分離用カララムにおいて、請求項1記載の式(1)で定義されるT S低数が0.25から1.0の範囲であることを特徴とする液体クロマトグラフィー用光学異性体分離用カララム。

【請求項7】 多機能誘導体担持充填剤を主たる構成要素とする液体クロマトグラフィー用光学異性体分離用カララムに供される充填剤である請求項1記載の式(1)で定義されるT S低数が0.25から1.0の範囲であることを特徴とする液体クロマトグラフィー用光学異性体分離用カララム。

【請求項8】 光学異性体分離を目的とする分析用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項9】 光学異性体分離を目的とする分析用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項10】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項11】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項12】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項13】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項14】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項15】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項16】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項17】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項18】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項19】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項20】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項21】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項22】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項23】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項24】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項25】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項26】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【請求項27】 逆相式液体クロマトグラフィーの分離用カララムである請求項6記載の液体クロマトグラフィー用光学異性体分離用カララム。

【0006】
 問題を解決するための手段】本発明者らは、多層誘導体を非等価性体分離用充填剤に関して鋭意研究を行った結果、本発明に達した。

【0007】即ち本発明は、多層誘導体担持花環剤を主たる構成要素とする液体クロマトグラフィー用光学異性体分離用充填剤において、当該充填剤をスラリー充填法

【式で、 V_e (ml) : カラム体積
 FR (ml/min.) : 流速
 $t(RS)$ (min.) : 流速
 $t(Blank)$ (min.) : カラムを保持しない状態でTSの溶出の溶出時間
 $t(Blank)$ (min.) : カラムを保持しない状態でTSの溶出の溶出時間
 を示す。】

【0009】
 【発明の実施の形態】以下、本発明の実施の形態について詳細に説明する。

【0010】本発明に用いられる多層誘導体は、多層と、その水酸基と反応する官能基を有する化合物とを反応させることによって得られる。

【0011】本発明に用いられる多層としては合成多層、天然多層及び天然物或多数の塊のいずれかを問わず、光学活性であるものでもよいが、好ましくは結晶性又は規則性の高いものが望ましい。例示すればβ-グルカン (セルロース)、α-1, 4-グルカン (アミロース、アミロペクチン)、α-1, 6-グルカン (デキストラン)、β-1, 6-グルカン (ブツラン)、β-1, 3-グルカン (例えばカーブラン、シフィラン等)、α-1, 3-グルカン、β-1, 2-グルカン (Crown Gel多層)、β-1, 4-ガラクトン、β-1, 2-アラビナン、α-1, 6-アラビナン、β-1, 4-アラビナン、α-1, 4-キシラン、β-1, 3-クタン (レビン)、β-1, 4-キシラン、β-1, 3-キシラン、β-1, 4-キシタン、α-1, 4-アセチルキシタン (キチン)、ブツラン、アガロース、アルギン酸等であり、アミロースを含有する炭粉も含まれる。これらの中では、高純度の多層を容易に入手できるセルロース、アミロース、β-1, 4-キシラン、β-1, 4-アラビナン、キチン、β-1, 4-アラビナン、イソリン、カードラン等が好ましく、特にセルロース、アミロースが好ましい。

【0012】これら多層の純平均重合度 (1分子中に含まれるヒドロキシル基あるいはヒドロキシ基の平均数) は5以上、好ましくは10以上であり、特に上開は、1000以下であることが取扱いの容易さの点で望ましい。

【0013】また水酸基と反応しうる官能基を有する化合物としてはイソシアナ基誘導体、カルボニル基、エステル基、炭化水素基、炭アミド化合物、ハロゲン化合物、アルデヒド、アルコールあるいはその他の酸基を有

によりカラム管に充填した液体クロマトグラフィー用光学異性体分離用カラムを用いて得られる下式 (1) で定義されるTS低数が0.25から1.0の範囲であることが特徴とする液体クロマトグラフィー用光学異性体分離用充填剤、並びにこれを充填したカラムを提供するものである。

【0008】
 $TS低数 = [Ve - t(Blank)] \times FR / [t(RS) - t(Blank)]$ × 100
 する化合物であればいかなるものでもよく、これらの阻害剤、防腐剤、芳香族、ヘテロ芳香族化合物を用いることができる。本発明に用いられる多層誘導体として特に好ましいのは、1グルコニドエニットあたり0.1個以上のグルタン結合又はエステル結合を有する多層のカラム担持誘導体あるいはエステル誘導体である。

【0014】本発明が多層誘導体担持充填剤とは、担持上に基布させた多層誘導体を原料に用い、担持と基布させた多層誘導体間の化学結合、担持上の多層誘導体同士の化学結合、第三成分を使用した化学結合、担持上の多層誘導体への光照射、γ線などの放射線照射、マイクロ波などの電波照射などによって引き起こされる反応、ラジカル開始剤などを用いるラジカル反応などによって、さらなる化学結合を形成せしめることで、より強い面花化を施された充填剤も含まれる。さらに担持上に基布させた多層誘導体を用いず、直接に多層、もしくは多層誘導体とシリカなどの担持を化学結合させる方法で作製される多層誘導体担持充填剤も含まれる。また、多層誘導体担持充填剤とする構成要素となる光学異性体分離用充填剤とは、上述の多層誘導体担持充填剤と他種の光学異性体分離用充填剤もしくは例えばオクタデシル表面処理されたシリカゲルなどの光学異性体分離用でない充填剤との混合物を書く。

【0015】本発明に用いられる担持としては、多孔質有機担体又は多孔質無機担体が挙げられ、好ましくは多孔質無機担体である。多孔質有機担体として適当なものには、ポリスチレン、ポリメタクリレート、ポリメタクリレート等からなる高分子物質であり、多孔質無機担体として適当なものは、シリカ、アルミナ、マグネシア、ガラス、カオリン、酸化チタン、ケイ酸塩、ヒドロキシアパタイトなどである。特に好ましい担持はシリカゲルであり、シリカゲルの粒径は0.1μm~1.0mm、好ましくは1μm~300μmであり、平均粒径は100Å~1000μm、好ましくは50Å~5000Åである。表面は、残存シリカゲルの影響を排除するために表面処理が施されていることが望ましいが、全く表面処理が施されていなくても問題ない。

【0016】本発明においてTS低数算出にあたっては、カラムを液体クロマトグラフ装置に接続した状態と接続しない状態におけるテストキス (トリメチルシリル) シラン (以下TSという) の溶出時間を測定し、得られた溶出時間を用い、上記式 (1) で定義されるTS

低数を算出する。この測定の際に用いられる分析装置はHPLC装置であり、使用される検出器としてはTSの溶出が確認できるRI検出器、UV検出器などがあるが、特にUV検出器を用い、波長210nmで検出することが好ましい。

【0017】分析条件としては順相条件、すなわち疎水性担持を主たる構成要素とする移動相条件下に実施する。具体的にはn-ヘキサノール/2-プロパノール=9/1 (v/v) の組成比の移動相である。また分析速度は室温 (25℃) であり、流速はカラム体積Vc (ml) の4分の1~9分の1、特に4.15分の1、すなわち [Vc × (1/4.15)] ml/min. が好ましい。さらにTSの打込み量は、移動相にTSを5.0mg/ml濃度で溶解させたTS溶液をカラム体積の300分の1~300分の1の体積量、特に415分の1の体積量、すなわち [Vc × (1/415)] ml打込むことが望ましい。

【0018】本発明においては、上記のようにして算出されたTS低数が0.25から1.0の範囲であることが必要であり、この範囲をはずれると良好な分離性能を得ることができない。

【0019】本発明の充填剤は、ガスクロマトグラフィー、液体クロマトグラフィー、超臨界クロマトグラフィー、薄層クロマトグラフィー、キャピラリー電気泳動などのクロマトグラフィー法及び膜分離による光学異性体分離に用いるのが一般的であるが、特に液体クロマトグラフィー法に適用するのが好ましい。

【0020】更に本発明の充填剤は、主として光学純度測定を目的とされる液体クロマトグラフィーの分析用カラム、数μg程度の光学活性取得を目的とする単カラム方式の液体クロマトグラフィーの分取用カラム、類似移動床方式に代表される連続式液体クロマトグラフィーの分取用カラム等に好ましく使用される。

【0021】
 【実施例】以下、本発明を実施例によって詳細に説明するが、本発明はこれら実施例に限定されるものではない。

【0022】実施例1
 TS低数=0.52のアミロース トリス (3, 5-ジメチルフェニルカルバメート) 担持光学異性体分離用充填剤の作製方法

① シリカゲル表面処理
 多孔質シリカゲル (粒径20μm、平均粒径1300Å) を公知の方法により、3-アミノプロピルトリエトキシランと反応させることによりアミノプロピルシリカゲル (APS処理) を施した。得られたAPS処理シリカゲルを3, 5-ジメチルフェニルカルバメートと反応させることで、カルバモイル表面処理が施されたシリカゲルを得た。

【0023】② アミロース トリス (3, 5-ジメチルフェニルカルバメート) の合成

ース10.0gを乾燥ビリン36.0ml中、3, 5-ジメチルフェニルイソシアネート8.2g (3当量) とビリン還流温度下、60時間加熱処理を行った後、メタノール6.0lに注ぎ込んだ。析出した固体はガラスフィルターで濾過し、メタノールで2回の洗浄後、真空乾燥 (80℃、5時間) を行った。その結果、若干黄色がかった白色固体3.5g (9.5%) が得られた。

【0024】③ アミロース トリス (3, 5-ジメチルフェニルカルバメート) のシリカゲルへの担持
 上記②で得たアミロース トリス (3, 5-ジメチルフェニルカルバメート) 10gを酢酸エチル100mlに溶解させ、このポリマー溶液の半量を均一に①のシリカゲル40gに塗布した。塗布後、酢酸エチルを50℃、120Torrの条件下で20分間の減圧乾燥を行い、さらに残り半量を同様に均一塗布後、先と同じ条件 (50℃、120Torr) で20分間の減圧乾燥を行うことで、目的のアミロース トリス (3, 5-ジメチルフェニルカルバメート) 担持型充填剤を得た。

【0025】④ 作製充填剤からのHPLC用充填剤への作製
 ⑤ 作製したアミロース トリス (3, 5-ジメチルフェニルカルバメート) をシリカゲル上に担持した分離用充填剤として用い、長さ25cm、内径0.46cmのステンレス製カラムにスラリー充填法で充填し、光学異性体用分離カラムを作製した。

【0026】実施例2
 TS低数=0.926のアミロース トリス (3, 5-ジメチルフェニルカルバメート) 担持光学異性体分離用充填剤の作製方法

① シリカゲル表面処理
 多孔質シリカゲル (粒径1300Å) にカルバモイル表面処理を施した。

【0027】② アミロース トリス (3, 5-ジメチルフェニルカルバメート) の合成
 実施例1の②と同様の手法により、アミロース トリス (3, 5-ジメチルフェニルカルバメート) を作製した。

【0028】③ アミロース トリス (3, 5-ジメチルフェニルカルバメート) のシリカゲルへの担持
 上記②で得たアミロース トリス (3, 5-ジメチルフェニルカルバメート) 52.5gを酢酸エチル489mlに溶解させ、このポリマー溶液の1/4量を均一に①のシリカゲル97.5gに塗布した。塗布後、酢酸エチルを50℃、120Torrの条件下で15分間の減圧乾燥を行い、さらに1/4量を同様に均一塗布後、先と同じ条件 (50℃、120Torr) で15分間の減圧乾燥を行った。引続き1/4量を均一塗布後、同条件 (50℃、120Torr) で45分間の減圧乾燥し、最後に残り1/4量を均一塗布後、同条件 (50℃、120Torr) で45

分間の減圧乾燥すること、目的のアミロース トリス (3, 5-ジメチルフェニルカルバメート) 担持型充填剤を得た。

【0029】⑨ 作製充填剤からのHPLC用充填剤の作製
 上記⑨で得たアミロース トリス (3, 5-ジメチルフェニルカルバメート) のシリカゲルへの担持

⑩で作製したアミロース トリス (3, 5-ジメチルフェニルカルバメート) をシリカゲル上に担持した分離剤を充填剤として用い、長さ2.5cm、内径0.46cmのステンレス製カラムにスラリー充填法で充填し、光学異性体用分離カラムを作製した。

【0030】実施例3
 T S係数=0.286のアミロース トリス (3, 5-ジメチルフェニルカルバメート) 担持光学異性体分離剤の作製方法
 ① シリカゲル表面処理
 実施例1の①と同じく、多孔質シリカゲル (粒径20μm、平均細孔径1300Å) にカルバモイル表面処理を施した。

【0031】⑩ アミロース トリス (3, 5-ジメチルフェニルカルバメート) の合成
 実施例1の⑩と同様の手法により、アミロース トリス (3, 5-ジメチルフェニルカルバメート) を作製した。

【0032】⑪ アミロース トリス (3, 5-ジメチルフェニルカルバメート) のシリカゲルへの担持
 上記⑩で得たアミロース トリス (3, 5-ジメチルフェニルカルバメート) 1.25gを酢酸エチル12.5mlに溶解させ、このポリマードープの全量を均一にシリカゲル1.25gに塗布した。塗布後、酢酸エチルを50℃、120Torrの条件下で15分間の減圧乾燥を行ったこと、目的のアミロース トリス (3, 5-ジメチルフェニルカルバメート) 担持型充填剤を得た。

【0033】⑫ 作製充填剤からのHPLC用充填剤の作製
 ⑬で作製したアミロース トリス (3, 5-ジメチルフェニルカルバメート) をシリカゲル上に担持した分離剤を充填剤として用い、長さ2.5cm、内径0.46cmのステンレス製カラムにスラリー充填法で充填し、光学異性体用分離カラムを作製した。

【0034】実施例4
 T S係数=0.696のアミロース トリス (3, 5-ジメチルフェニルカルバメート) 担持光学異性体分離剤の作製方法
 ① シリカゲル表面処理
 実施例1の①と同じく、多孔質シリカゲル (粒径20μm、平均細孔径1300Å) にカルバモイル表面処理を施した。

【0035】⑫ アミロース トリス (3, 5-ジメチルフェニルカルバメート) の合成
 実施例1の⑩と同様の手法により、アミロース トリス (3, 5-ジメチルフェニルカルバメート) を作製した。

【0036】⑬ アミロース トリス (3, 5-ジメチルフェニルカルバメート) のシリカゲルへの担持
 上記⑫で得たアミロース トリス (3, 5-ジメチルフェニルカルバメート) 2.70gを酢酸エチル27.0mlに溶解させ、このポリマードープの1/2量を均一にシリカゲル1.50gに塗布した。塗布後、酢酸エチルを50℃、120Torrの条件下で15分間の減圧乾燥を行った。引続きポリマードープの1/2量を同様に塗布した。引続き、下記の計算式によってT S係数を算出した。結果を表1に示す。

移動相: n-ヘキサン/2-プロパノール=9/1 (v/v)
 流速: 1.0ml/min.
 温度: 25℃
 検出: 210nm
 打込みT S係数: 5.0mg/ml (移動相)
 T S係数計算式:

$$T S = \frac{0.23 \times 0.23 \times 3.14 \times 25}{4 \times 15 \times 1.0} \times \frac{1.0}{1.0} = 0.16$$

$$T S_{\text{係数}} = \frac{[4.15 - (1.05) - 0.16]}{[1.05] - 0.16} \times 1.0$$

さらに実施例1～5及び比較例1～2において作製したHPLC用光学異性体分離剤用カラムを用い、ラセミ体である下記式で表される化合物1～4の光学分離を行い、下記式により、各光学異性体の分離の程度を示す指標である分離度R S値を算出した。その結果も表1に示す。

【0051】
 【化1】

を充填剤として用い、長さ2.5cm、内径0.46cmのステンレス製カラムにスラリー充填法で充填し、光学異性体用分離カラムを作製した。

【0042】比較例1
 T S係数=1.05のアミロース トリス (3, 5-ジメチルフェニルカルバメート) 担持光学異性体分離剤の作製方法
 ① シリカゲル表面処理
 実施例1の①と同じく、多孔質シリカゲル (粒径20μm、平均細孔径1300Å) にカルバモイル表面処理を施した。

【0043】⑫ アミロース トリス (3, 5-ジメチルフェニルカルバメート) の合成
 実施例1の⑩と同様の手法により、アミロース トリス (3, 5-ジメチルフェニルカルバメート) を作製した。

【0044】⑬ アミロース トリス (3, 5-ジメチルフェニルカルバメート) のシリカゲルへの担持
 上記⑫で得たアミロース トリス (3, 5-ジメチルフェニルカルバメート) 2.5gを酢酸エチル18.75mlに溶解させ、このポリマードープの1/4量を均一にシリカゲル3.75gに塗布した。塗布後、酢酸エチルを50℃、120Torrの条件下で15分間の減圧乾燥を行った。引続きポリマードープの1/4量を同様に塗布した。さらに、ポリマードープの1/4量を同様に塗布後、酢酸エチルを同条件にて30分間の減圧乾燥を行った。最後に、下記の計算式によってT S係数を算出した。結果を表1に示す。

移動相: n-ヘキサン/2-プロパノール=9/1 (v/v)
 流速: 1.0ml/min.
 温度: 25℃
 検出: 210nm
 打込みT S係数: 5.0mg/ml (移動相)
 T S係数計算式:

$$T S = \frac{0.23 \times 0.23 \times 3.14 \times 25}{4 \times 15 \times 1.0} \times \frac{1.0}{1.0} = 0.16$$

$$T S_{\text{係数}} = \frac{[4.15 - (1.05) - 0.16]}{[1.05] - 0.16} \times 1.0$$

さらに実施例1～5及び比較例1～2において作製したHPLC用光学異性体分離剤用カラムを用い、ラセミ体である下記式で表される化合物1～4の光学分離を行い、下記式により、各光学異性体の分離の程度を示す指標である分離度R S値を算出した。その結果も表1に示す。

【0051】
 【化1】

【0047】⑫ アミロース トリス (3, 5-ジメチルフェニルカルバメート) の合成
 実施例1の⑩と同様の手法により、アミロース トリス (3, 5-ジメチルフェニルカルバメート) を作製した。

【0048】⑬ アミロース トリス (3, 5-ジメチルフェニルカルバメート) のシリカゲルへの担持
 上記⑫で得たアミロース トリス (3, 5-ジメチルフェニルカルバメート) 2.70gを酢酸エチル27.0mlに溶解させ、このポリマードープの1/2量を均一にシリカゲル1.50gに塗布した。塗布後、酢酸エチルを50℃、120Torrの条件下で15分間の減圧乾燥を行った。引続きポリマードープの1/2量を同様に塗布した。引続き、下記の計算式によってT S係数を算出した。結果を表1に示す。

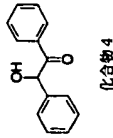
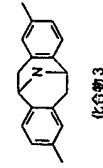
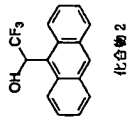
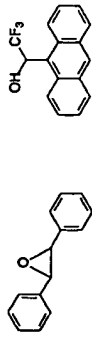
移動相: n-ヘキサン/2-プロパノール=9/1 (v/v)
 流速: 1.0ml/min.
 温度: 25℃
 検出: 210nm
 打込みT S係数: 5.0mg/ml (移動相)
 T S係数計算式:

$$T S = \frac{0.23 \times 0.23 \times 3.14 \times 25}{4 \times 15 \times 1.0} \times \frac{1.0}{1.0} = 0.16$$

$$T S_{\text{係数}} = \frac{[4.15 - (1.05) - 0.16]}{[1.05] - 0.16} \times 1.0$$

さらに実施例1～5及び比較例1～2において作製したHPLC用光学異性体分離剤用カラムを用い、ラセミ体である下記式で表される化合物1～4の光学分離を行い、下記式により、各光学異性体の分離の程度を示す指標である分離度R S値を算出した。その結果も表1に示す。

【0051】
 【化1】

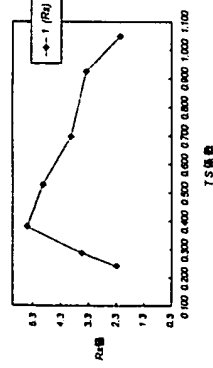


【0052】 $R_s = 2$ (t1-t2) / (W1+W2)
(ここで、t1、t2は各光学異性体の検出時間、W1、W2は
光学異性体ピークのピーク幅を示す。)
【0053】
【表1】

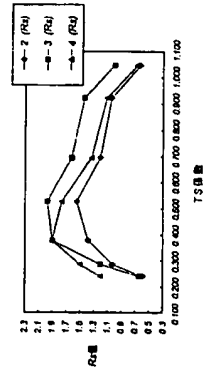
HPLC用 カラム	t(TS) (min)	分離度 (Rs)			
		化合物1	化合物2	化合物3	化合物4
実 験 1	2.67	4.91	1.55	1.98	1.77
実 験 2	2.15	3.40	1.05	1.44	1.12
実 験 3	3.14	3.55	1.03	1.21	1.50
実 験 4	2.42	3.95	1.21	1.63	1.34
実 験 5	2.94	3.79	1.38	1.90	1.91
比 較 例 1	2.03	1.050	2.17	0.63	1.01
比 較 例 2	3.25	0.240	2.28	0.59	0.65
					1.21

【0054】また充填剤のTS係数と化合物1のR_s値との関係を図1に、充填剤のTS係数と化合物2～4のR_s値との関係を図2に示した。
【0055】以上の結果から、TS係数が0.25から1.0の範囲にある充填剤は、光学異性体の分離性能が良好であることがわかる。

【図1】



【図2】



フロントページの続き
(51)Int. Cl.⁷
C 07 C 29/76
33/40
45/79
49/83
Z

識別記号

F I
C 07 C

J-コード (3桁)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.